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specification e.g. on page 7, third paragraph). Claim 16 has been cancelled. Claims 1-15 and 17-21 are now pending. It is believed that no new matter has been added.

35 U.S.C. 112, first paragraph rejection

Claims 1, 2, 4-8 and 11-15 were rejected by the examiner as being non-enabling for the treatment of rosacea and coperose. In response to the applicants' previous arguments, the examiner responded that "...the Applicant has to submit *an evidence* that the NO-synthase inhibitors are, in fact, effective in preventing rosacea and couperose.".

However, based upon the examiner's development of her non-enablement rejection based upon her *Wands*-type analysis (see MPEP 2164.01(a)), there does not appear to a basis for a requirement for a submission of "evidence". It is noted that not only does the MPEP not require that "evidence" be present in the specification, in certain instances it is not even necessary for the subject matter of the claimed invention to be recited in the specification if the subject matter was present in the claim as originally filed and the limitation in and of itself may enable one skilled in the art to make and use the claim containing the limitation (see last paragraph of MPEP 2164).

MPEP 2164.01 (Test of Enablement), in addition to defining the standards upon which enablement is to be based (see *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), also states that "'The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patient coupled with information known in the art without undue experimentation.' A patent need not teach, and preferably omits, what is well known in the art.(citations omitted)"

Most importantly, MPEP 2164.01 also teaches that "Determining enablement is a question of law ***based on underlying factual findings*** (bold and italics added by author). *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The examiner's original lack of enablement rejection as it was presumed to apply to the undue experimentation factors from MPEP 2164.01(a) is listed below (examiner's comments in bold and quotation marks):

Factor	Examiner's statement
(A) The breadth of the claims;	**Not addressed**
(B) The nature of the invention;	**"The burden of enabling the prophylaxis or prevention of a disease (i.e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition."**
(C) The state of the prior art;	**Not addressed**
(D) The level of one of ordinary skill in the art;	**Not addressed**
(E) The level of predictability in the art;	**Not addressed**
(F) The amount of direction provided by the inventor;	**"Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to rosacea and couperose."**
(G) The existence of working examples; and	**Not addressed**
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.	**"Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention."**

As can be seen from the chart above, only three of the eight undue experimentation factors have been addressed. Furthermore, even with the three factors which have been addressed, each appear to be pronouncements made by the examiner, i.e. there is no indication that the statements made were based upon "underlying factual findings". The requirement for factual findings is even more relevant in the

present case as it has previously been held that there is enablement for the treatment of rosacea and couperose ***and*** the specification indicates that patients previously afflicted with rosacea and/or cuperose do not have a recurrence of the condition(s) when treatment is continued (i.e. was prevented), see page 6, second to last paragraph of specification.

Although the examiner would be justified in rescinding this rejection based upon the above arguments, if this is the only issue remaining which prevents an allowance of the pending claims, in order to expedite prosecution of the application, the examiner may delete reference to prophylaxis in an examiner's amendment; the applicants' reserve the right to resubmit the broader claim as part of a divisional application.

35 U.S.C. 102(b) rejection

Claims 1-4, 7-11 and 14-16 (now 1-4, 7-9, 11 and 14-16 after amendment) were rejected by the examiner as being anticipated by Giacomoni (WO 96/26711).

It is requested that the examiner reconsider the arguments made in the response dated 22 April 2002 and also the additional arguments made below:

without consideration of amendment

The examiner stated in the Response to Arguments-section that "The compositions of Giacomoni are used for the treatment of rosaceous acne...The applicant is reminded that the reference's disclosure is not limited to examples or preferred embodiments and must be considered as a whole. Thus, Giacomoni explicitly teach treating rosaceous acne with compositions containing a NO-synthase inhibitor in combination with a retinoid."

While the applicants agree that the teachings of a reference must be considered "as a whole", the applicants disagree with what the "as a whole" determination means within the context of Giacomoni.

First, Giacomoni narrowly directs the reader towards four specific NO-synthase inhibitors (i.e. NMMA, NAME, NNA and ADMA – see bottom of 4th page of translation) ***and*** for a specific type of NO-synthase (i.e. constitutive NO-synthase and "more particularly to the inhibition of NO-synthase in the endothelial cells" – see bottom of 4th page of translation).

Second, as stated by the examiner, the use of an NO-synthase inhibitor requires the presence of a retinoid ***and*** is buried within a Markush group of potential uses (sixteen specific categories ("genuses") which bridge between pages 7 and 8 of the translation of which rosaceous acne is but a species of one of the sixteen genuses.). There is no guidance or teaching within Giacomoni which teaches or suggests the use of a retinoid with an NO-synthase inhibitor and had the Giacomoni reference been examined as a U.S. application, it is conceivable that the assertion of potential use would have been written off as an "invitation to experiment" rather than being an indicator of possession of an inventive concept. MPEP 2131 states that to anticipate a claim, the reference must teach every element of the claim and quotes from *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d, 1913, 1920 (Fed. Cir. 1989) which states "***The identical invention must be shown in as complete detail as is contained in the...claim.***" The applicants hold that the Giacomoni reference does not meet this standard.

with consideration of amendment

Even if *in arguendo* the Giacomoni reference were anticipatory for NMMA, NAME, NNA and ADMA, Giacomoni is not anticipatory for the specific compounds which are cited in claims 3, 9, 10 and 19-21.

35 U.S.C. 103(a) rejection

Claims 5, 6, 12 and 13 were rejected by the examiner as being obvious over Giacomoni (WO 96/26711) in view of either Breton et al. (U.S. Patent 5,795,574) or Ptchelintsev et al. (U.S. Patent 5,847,003).

It is requested that the examiner reconsider the arguments made in the response dated 22 April 2002 and also the additional arguments made above in response to the examiner's 102(b) rejection.

Closing

The applicants believe the claims are in condition for allowance. However, should any minor issue arise which prevents allowance of the application, the examiner is encouraged to call the undersigned at the telephone number below.

Respectfully submitted,
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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the foregoing Amendment Under 37 CFR § 1.111 (8 pages total) is being facsimile transmitted to the United States Patent and Trademark Office on the date indicated below:

Date: **30 September 2002**

By: _____
Vilma I. Fernandez

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COPY OF CLAIMS SHOWING AMENDMENTS MADE

1. A method for the prophylaxis and treatment of rosacea and couperose which comprises applying to a patient in need thereof an effective amount of one compound or two or more compounds selected from the group consisting of NO-synthase inhibitors and **[derivatives]** ***salts*** thereof.

3. Cosmetic or dermatological topical preparations comprising **[a content of one compound or two or more compounds selected from the group consisting of]** ***a*** NO-synthase inhibitor**[s and derivatives thereof]** ***or salts thereof are selected from the group consisting of L-MEA, 2-Iminobiotin, L-NIO, S-Methylisothiourea sulphate, S-Methyl-L-thiocitrulline, L-NIL, 7-Nitroindazole, PBITU, L-Thiocitrulline, alpha-N-acetyl-L-NAME and salts thereof***.

9. Cosmetic or dermatological topical preparations according to Claim 3, wherein said NO-synthase inhibitor**[s and derivatives are selected from the group consisting of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof]** ***or salts thereof is selected from the group consisting of 2-Iminobiotin, L-NIO, S-Methylisothiourea sulphate, S-Methyl-L-thiocitrulline, L-NIL, 7-Nitroindazole, PBITU, L-Thiocitrulline, and salts thereof***.

10. Preparation according to Claim 9, wherein said **[compound is N^G-nitro-L-arginine methyl ester or N^G-nitro-L-arginine methyl ester hydrochloride]** ***NO-synthase inhibitor or salts thereof further comprises L-NAME***.